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Evaluation of QT Interval Duration and Dispersion and Proposed Clinical Criteria in Diagnosis of Long QT Syndrome in Patients With a Genetically Uniform Type of LQT1

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Objectives. **This study investigated the ability of QT duration, QT dispersion (QTD) and clinical diagnostic criteria to correctly identify genetically documented LQT1 type long QT syndrome (LQTS) patients, and to separate symptomatic and asymptomatic LQT1 patients.**

Background. **Ventricular repolarization has played an essential role both in diagnosis and risk assessment of LQTS. Today, molecular genetic techniques permit unequivocal identification of many LQTS patients.**

Methods. **QT interval and QTD in 12 symptomatic and 18 asymptomatic LQT1 patients and their 43 healthy relatives were evaluated. The sensitivity and specificity of upper normal limits of QT interval, two QT interval adjustment methods (Bazett's and Fridericia's formulas), and the proposed clinical criteria for LQTS were assessed. Occurrence of a mutant (D188N) KVLQT1 gene was considered as the basis of classification into affected and nonaffected individuals.**

Results. **Diagnostic sensitivity and specificity values were 90% and 88% using Bazett's formula, and 80% and 100% using Fridericia's cubic root formula or upper normal limits for QT interval. Suggested diagnostic criteria for LQTS reached 100% specificity, but 47% of the DNA-documented LQT1 patients were classified into the category of low or intermediate probability of LQTS. QT interval and heart rate did not differ between symptomatic (464 ± 47 ms, 70 ± 9 min^{-1}) and asymptomatic 460 ± 41 ms, 65 ± 13 min^{-1}) LQT1 patients. QTD was increased in symptomatic LQT1 patients compared to unaffected relatives (66 ± 48 vs. 37 ± 15 ms, p = 0.02), but symptomatic patients LQT1 did not differ from asymptomatic (45 ± 19 ms).**

Conclusions. **Not all LQT1 patients can be distinguished from healthy relatives by assessment of QT duration or clinical criteria. Presence of LQT1 gene can carry the risk of cardiac events even with no or only marginal prolongation of QT interval.**

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Congenital long QT syndrome (LQTS) is most often inherited in an autosomal dominant trait and is associated with malignant arrhythmias (1–3). The diagnosis is usually based on prolongation of ventricular repolarization time but linkage studies have shown that QT interval duration alone may not be sufficient for correct diagnosis (4,5). Therefore, additional diagnostic criteria have been proposed to classify the borderline cases (6,7). One of the confounding factors leading to misdiagnosis may be the heart rate correction of QT interval. Indeed, the adequacy of the most widely used formula to adjust the QT interval for heart rate has been questioned (8–10). Theoretically, the drawbacks of QT adjustment may also have caused a selection bias in studies carried out among LQTS patients since the inclusion criteria in various studies have usually been based on the QT interval alone or combined with other diagnostic criteria.

Identification of both symptomatic LQTS patients as well as their asymptomatic affected relatives is important as they are known to be at increased risk of cardiac events (11–13). The risk of events in LQTS, including syncope or sudden death, has been related to the extent of QT interval duration (14). In addition to prolonged QT interval, QT dispersion, a measure of repolarization inhomogeneity (15), is one of the parameters that can be measured from surface electrocardiogram (ECG) and might serve as an indicator of increased risk of arrhythmic events (15). In addition, QT dispersion has been suggested to be a predictor of therapeutic efficacy in LQTS (16). However, as LQTS is a genetically heterogeneous disorder with multiple ion channel pathologies (17–20), the utility of the risk markers may vary in different subtypes of LQTS.

Identification of the disease-causing mutation of the cardiac potassium channel gene KVLQT1 in a very large family (5) has now permitted us to compare the repolarization parameters in DNA-documented carriers of the mutation and their healthy relatives. First, as the diagnosis of LQTS was based on molecular genetic analysis and not on QT interval measure-

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Abbreviations and Acronyms

DNA = Deoxyribonucleic acid
ECG = Electrocardiogram, electrocardiographic
LQTS = Long QT syndrome
LQT1 = LQT1 type of long QT syndrome
QT_c = QT interval corrected with the square root formula ($QT/RR^{1/2}$)
QTD = QT dispersion
QT_{fc} = QT interval corrected with the cubic root formula ($QT/RR^{1/3}$)
QTm = QT interval measured from QRS onset to T wave peak
rQTD = Relative QT dispersion

ments, we compared the distribution of QT intervals in LQT1 patients to those in healthy relatives and to population-based normal upper limits. Second, we assessed the sensitivity and specificity of the commonly used normal upper limit of QT interval (440 ms), together with different correction algorithms as well as the proposed clinical diagnostic criteria (6) in identifying carriers of the mutation. Third, we examined whether the duration of QT interval or increased dispersion of QT could distinguish symptomatic from asymptomatic patients within this genetically defined population.

Patients and Methods

The study group consisted of members of a family in which a large number of individuals were identified to be carriers of a mutant KVLQT1 gene causing LQTS type 1 (LQT1). Identification of the mutation and the pedigree has been presented earlier (5). In brief, the proband of the family was a 10-year old girl who was subjected to cardiologic examinations because of a syncope upon running. In addition to the proband and her mother, 28 relatives were found to be carriers of a substitution of asparagine for aspartic acid at codon 188 of the KVLQT1 gene (5). This mutation (D188N) is localized to the pore-S6 region of the KVLQT1 channel, substitutes a conserved amino acid residue and destroys an existing BsmFI restriction site in the KVLQT1 gene, thus permitting its convenient analysis by polymerase chain reaction (PCR) followed by restriction enzyme digestion (5). The physicochemical nature of the mutation, its cosegregation with the LQTS phenotype in the index family and its absence in a large number of random controls provide convincing evidence for its disease-causing role (5).

Twelve of the patients in LQT1 group had experienced an exercise-related syncope. The youngest symptomatic patient was 3 years old at the time of the first syncope. Eight patients had experienced syncope at the age of 5 to 25 years and 3 patients between 30 to 37 years. In addition to them, one boy was drowned at the age of 10. Although not studied for DNA, he was included in the study group since his QTc was 450 ms, he had been treated for LQTS because of multiple exercise-related syncopal attacks before his death and his mother is a carrier of the D188N mutation.

Table 1. Clinical and Electrocardiographic Characteristics of LQT1 Patients and Controls

	LQT1	Controls	p Value
Number of subjects	30	43	
Mean age (years)	36 ± 19	44 ± 20	NS
Age range (years)	11–69	7–72	
Men/women	10/20	22/21	NS
Resting heart rate min^{-1}			
Without betablockers	68 ± 12 (n = 23)	68 ± 12 (n = 41)	NS
On betablocker therapy	64 ± 9 (n = 7)	78 (n = 1)	
QT interval (ms) (lead II)	461 ± 41	381 ± 33	<0.001
QT_c interval (ms) (lead II)	484 ± 38	404 ± 25	<0.001

NS = not significant, $QT_c = QT/RR^{1/2}$ (23).

As a control group, we studied 44 noncarriers of the mutation from the same pedigree. One diabetic subject was excluded from the study because diabetes mellitus may affect the repolarization time (21). Seven LQT1 patients (5 symptomatic, 2 asymptomatic) and one control subject were receiving beta-adrenergic blocking agents during the time of ECG registration. In two cases (both LQT1 patients) beta-adrenergic antagonists had been discontinued for at least five half-lives before ECG was obtained. No other medications known to affect the repolarization were in use. Clinical characteristics of the LQT1 patients and controls are summarized in Table 1. The study was approved by the institutional review committee and was in accordance with the institutional guidelines. An informed consent was obtained from all patients and controls.

ECG analysis. All patients and controls had standard 12-lead electrocardiogram (ECG) recorded at paper speed 50 mms^{-1} and amplification of 0.1 mV/mm. ECG measurements were carried out by one investigator who was unaware of the genotypes of subjects. All subjects were in sinus rhythm, and no one had atrioventricular or bundle branch block. Heart rate was calculated from the three RR intervals preceding the measured QT intervals. QT intervals were measured manually from the onset of the QRS complexes to the end of T wave defined as the intersection of isoelectric line and the tangent of maximal downward limb of the T wave (22). The early phase of repolarization (QTm) was measured from the onset of QRS complex to the apex of T wave in each lead. In cases with notched or double peaked T wave, the first peak was chosen for QTm measurement. Each registered measurement was a mean of two consecutive QT intervals in each lead. If the amplitude of T wave was low (<0.1 mV), the lead was excluded from the analysis.

QT dispersion (QTD) was defined as the difference between the maximal and minimal QT interval in any of the leads measured. Relative QT dispersion (rQTD) was calculated as follows: (the SD of QT/mean QT) × 100. Relative QTm dispersion (QTmD) was defined as (the SD of QTm/mean QTm) × 100.

At least 9 leads were available for measurements in each

subject. QT interval was adjusted for subject's heart rate using Bazett's formula ($QT_c = QT/RR^{1/2}$ (sec) (23). In order to compare the sensitivity and specificity of different methods to adjust for heart rate in separating LQT1 patients from their healthy relatives, we also calculated corrected QT intervals (QT_{fc}) adjusted for heart rate by the Fridericia's cubic root formula ($QT_{fc} = QT/RR^{1/3}$) (24). In addition to these adjustment methods, unadjusted QT values were also compared to upper normal limits for both genders. As the upper reference limit, we used the mean plus 1.96 standard deviation (SD) estimated at specific heart rates in a large survey of 10717 middle-aged Finnish subjects (25). Measurements from lead II were used for comparisons between these normal values and different heart rate corrected QT intervals.

Application of proposed clinical criteria. We also divided patients into three probability groups according to the proposed clinical criteria for diagnosing LQTS (6). These criteria take into account the ECG findings, clinical history and family history. QT_c values equal to or exceeding 480 $ms^{1/2}$ are assigned a value of 3 points and QT_c 460–470 $ms^{1/2}$ 2 points (for males, even QT_c 450 $ms^{1/2}$ 1 point); torsades de pointes *or* stress-related syncope 2 points (syncope without stress 1 point), T-wave alternans and/or notched T wave in three leads 1 point each, and for children, resting heart rate lower than the second percentile for age 0.5 point. Congenital deafness increases the score by 0.5 point, sudden cardiac death before the age of 30 years among immediate family members by 0.5 point *or* presence of family members with definite LQTS (score ≥ 4), by 1 point. According to the proposed criteria, patients receiving 0 to 1 points have low, those with 2 to 3 points intermediate, and individuals receiving 4 or more points, high probability of LQTS.

Statistical analysis. Data are presented as mean ± 1 SD. Comparisons between two groups were performed by two-tailed Student *t* test for unequal or equal variances where appropriate, and differences among symptomatic and asymptomatic LQT1 patients and controls were assessed by one-way analysis of variance and by Scheffe's test, or Mann-Whitney U-test if the between-groups variances differed significantly. For dichotomous variables chi-square test was used. The correlation between QT and QT dispersion indexes was evaluated using linear regression analysis. A p value of <0.05 was considered as significant.

Results

QT interval measurements. Demographic and electrocardiographic characteristics of all 30 LQT1 patients and controls are summarized in Table 1. No gender-related differences were seen in resting heart rates (patients with beta blocking medication excluded), or mean, maximal or minimal QT intervals among the LQT1 patients or within control group. Figure 1 shows the actual QT intervals in relation to heart rates in both study groups. The mean of all QT interval estimates were longer among LQT1 patients, whether symptomatic or asymptomatic than in controls (Table 2). All the parameters presented in Table 2 were reevaluated after exclusion of patients with beta blocking medication, and differences between the patients and controls remained. Both actual and rate-adjusted QT interval parameters presented (Table 2) as well as QTm values were similar in symptomatic and asymptomatic LQT1 patients. There was some overlapping of the individual QT_c and QT_{fc} values between symptomatic and asymptomatic LQT1 patients and controls (Fig. 2). Frequency of symptomatic patients in the subset of LQT1 patients with QT_c >476 ms (median of all affected individuals) did not differ significantly from those with QT_c <476 ms.

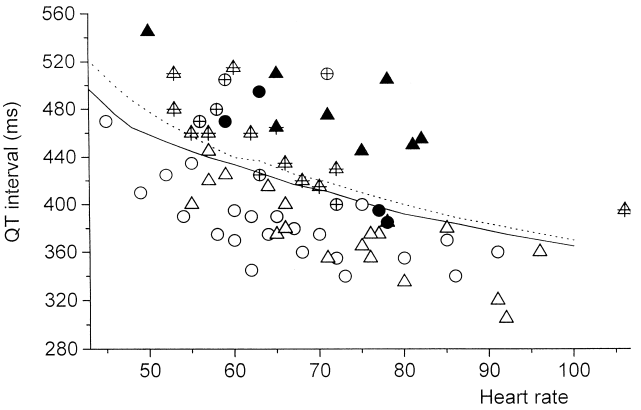


Figure 1. Distribution of QT intervals according to heart rate. Provisional normal upper limits for QT interval derived from a study on population (25) are marked for men (**solid line**) and for women (**dashed line**).
○ controls, men
△ controls, women
⊕ LQT1, men, symptom −
⟑ LQT1, women, symptom −
● LQT1, men, symptom +
▲ LQT1, women, symptom +

Dispersion of repolarization. Dispersion of QT in symptomatic LQT1 patients was increased (66 ± 48 ms) compared to controls (45 ± 19 ms, p = 0.02). The mean value for dispersion of QT in the asymptomatic LQT1 patients did not

Table 2. Total and Early Duration of Repolarization and Heart Rate Corrected QT Intervals in Symptomatic and Asymptomatic LQT1 Patients and Controls

	Symptomatic LQT1 (n = 12)	Asymptomatic LQT1 (n = 18)	Controls (n = 43)	p Value
HR (beats/min)	70 ± 9	65 ± 13	69 ± 12	NS
QT (lead II)	464 ± 47	459 ± 38	381 ± 33	<0.001*
QTmean	472 ± 46	460 ± 41	379 ± 33	<0.001*
QTmin	439 ± 44	434 ± 42	358 ± 32	<0.001*
QTmax	506 ± 66	479 ± 47	395 ± 37	<0.001*
QT_c (lead II)	496 ± 38	475 ± 36	404 ± 25	<0.001*
QT_{fc} (lead II)	485 ± 38	469 ± 31	396 ± 22	<0.001*
QTm (lead II)	391 ± 44	380 ± 33	310 ± 32	<0.001*

HR = heart rate, QT = measured QT interval. QTmin, QTmean, QTmax = minimal, mean and maximal QT interval measured from 12-lead ECG. $QT_c = QT/RR^{1/2}$, $QT_{fc} = QT/RR^{1/3}$, QTm = early duration of repolarization, * = symptomatic LQT1 patients vs. controls, and asymptomatic LQT1 patients vs. controls.

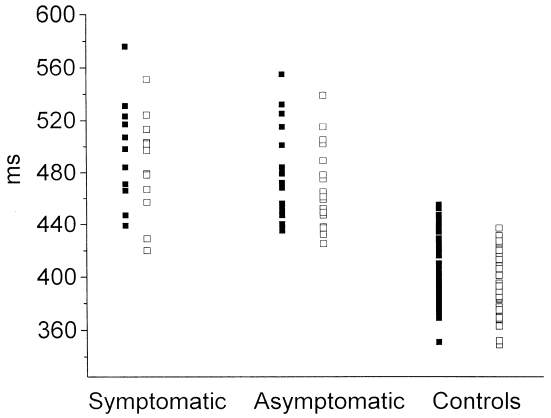


Figure 2. QT intervals adjusted according to Bazzet's formula (QT_c) (23) and Fridericia's cubic root formula (QT_{fc}) (24) for symptomatic and asymptomatic LQT1 patients and controls.
■ QT_c
□ QT_{fc}

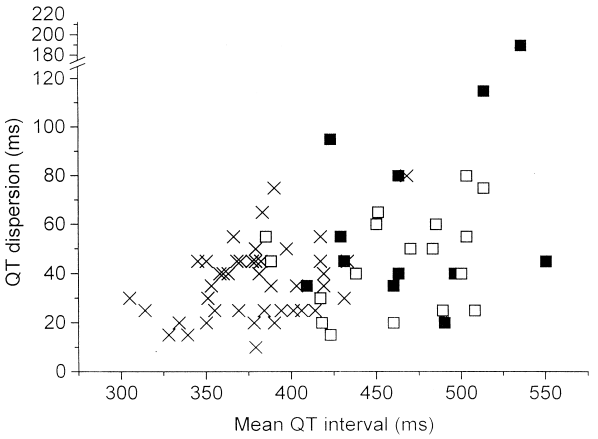
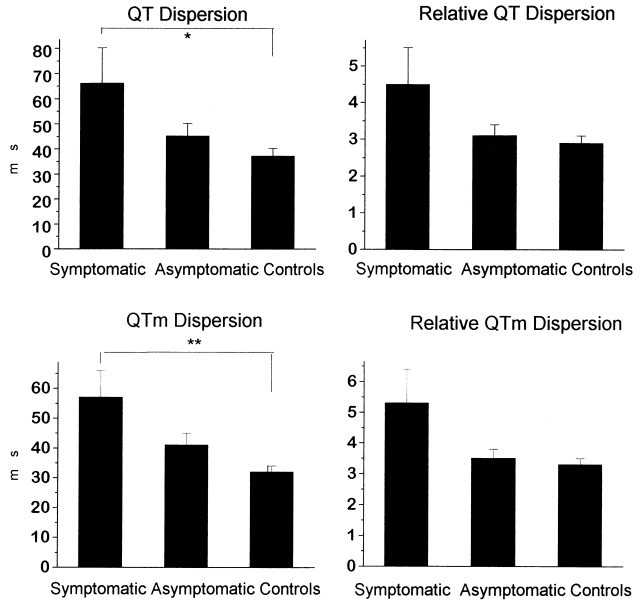


Figure 4. Relation of QT dispersion and heart rate.
■ LQT1 symptomatic
□ LQT1 asymptomatic
× Controls

differ significantly from that in the symptomatic or in the control individuals (Fig. 3). QT dispersion and mean QT did not correlate significantly with each other in LQT1 patients ($r = 0.34$, $p = 0.07$) or controls ($r = 0.28$, $p = 0.64$). Relationship between QT dispersion and mean QT is shown in Figure 4. Dispersion of early phase of repolarization (QTm) was increased in the group of symptomatic LQT1 patients (57 ± 32 ms) compared to controls (32 ± 15 ms, $p = 0.006$), whereas asymptomatic patients and control individuals did not differ significantly in this respect (Fig. 3). Relative dispersion of early phase of repolarization (rQTm) did not differ significantly between any of the three groups, however (Fig. 3). After exclusion of patients with beta blocking medication, the relative dispersion of early phase of repolarization differed significantly between symptomatic LQT1 patients and controls (5.2 ± 2.9 versus 3.3 ± 1.4, $p = 0.02$).

Figure 3. Mean dispersion values for total duration of ventricular repolarization (QT dispersion, upper left panel), early duration of ventricular repolarization (QTm dispersion, lower left panel) and corresponding relative QT and QTm dispersions (upper right and lower right panels, respectively) for symptomatic and asymptomatic LQT1 patients and controls. SEM indicated above the bars.



Performance of QT measures and proposed clinical diagnostic criteria in revealing the genotype. We evaluated the sensitivity and specificity of two different QT adjustment formulas (23,24) to correctly diagnose the carriers of the KVLQT1 mutation. QT intervals adjusted for heart rate according to Bazett's square root formula or Fridericia's cubic root formula exceeding 440 ms were considered abnormal. Second, the sensitivity and specificity of the provisional normal upper limits for QT interval obtained in a large Finnish population survey were assessed. Third, the application of proposed diagnostic criteria for LQTS (6) in the present KVLQT1 population was tested. The distribution of QT intervals at different heart rates according to genotype and gender is shown in Figure 1. The division of gene carriers and noncarriers into affected and nonaffected according to QT interval adjustment methods, normal values or diagnostic criteria are presented in Table 3. Diagnostic sensitivity and specificity based on Bazett's formula were 90% and 88%, respectively, while assessment by heart rate-adjusted QT intervals according to the Fridericia's cubic root formula yielded sensitivity of 80% and specificity of 100%. Classification according to the normal upper limit (mean ± 2 SD) of QT interval obtained from a large population study (25) resulted in a sensitivity of 80% and specificity of 100%. Application of the renewed diagnostic criteria for LQTS (6) to our study population reached 100% specificity, but of the affected, 27% were classified into the category of low probability, 20% into category of intermediate probability and only 53% to the category of high probability of LQTS.

Table 3. Application of Various Diagnostic Alternatives in LQTS in Regard to Molecular Classification of Patients and Their Relatives

Diagnostic Classification	Genetic Status	
	D188N +	D188N −
Bazett (23)		
QT_c <440 ms	3	38
QT_c >440 ms	27	5
Fridericia (24)		
QT_{fc} <440 ms	6	43
QT_{fc} >440 ms	24	0
Population study (25)		
QT < upper normal limit	6	43
QT > upper normal limit	24	0
Proposed diagnostic criteria for the LQTS (6)		
Low probability	8	43
Intermediate probability	6	0
High probability	16	0

Discussion

Our results show that overlapping of QT interval durations occurs between LQTS patients and normal population, irrespective of method used to judge QT interval normality. Thus, a standard 12-lead ECG is an insufficient method to diagnose all affected LQTS patients, even in a genetically homogenous population. There is an urgent need for accurate methods that would minimize the number of borderline cases when suspecting LQTS.

QT duration. In this study the duration of ventricular repolarization in symptomatic and asymptomatic LQT1 patients with the same genotype was similar. This is a disquieting finding but may only seemingly contrast the prevailing view of the predictive importance of length of QT interval as such. Previous large family studies (3) and investigations in children with LQTS (14) have shown that the longer the duration of ventricular repolarization, the higher the risk of cardiac events. In the former study, the family members with $QT_c \leq 440$ ms were defined as unaffected and their risk of cardiac events proved too low (3); however, in lack of molecular diagnosis of LQTS this study (3) does not tell the exact risk of malignant arrhythmias of LQTS gene carriers with QT_c <440 ms. Moreover, it is likely that in both studies cited above (3,14) individual families have been heterogeneous in terms of the causative genes and mutations. Since certain families have shown to have had a more malignant course than on the average (26), it is possible that certain LQTS mutations are more virulent than others. This does not necessarily imply that a family member with a specific mutation and a marginally prolonged QT interval in standard 12-lead ECG has a lower risk than a relative whose QT prolongation is more substantial because a carrier status of a specific mutation itself seems to be the major determinant of cardiac events.

QT dispersion. We found that the dispersion of ventricular repolarization was increased in symptomatic LQTS patients. Increased dispersion of the QT interval in patients with LQTS has been reported in several earlier studies without performing molecular diagnosis (16,27,28). However, conclusions on the relationship between degree of dispersion and risk of cardiac events have been inconsistent. The study by Linker et al. (28) showed no difference in the degree of dispersion between LQTS groups with frequent or infrequent symptoms whereas Priori et al. found that LQTS patients who responded to beta-blockade had lower QT dispersion than nonresponders while on beta-adrenergic antagonists therapy (16). In our molecularly defined cohort of LQTS patients, overlapping of QT dispersion between groups was considerable (Fig. 4) and accordingly in the individual risk assessment the value of QT dispersion appears to be low.

Clinical diagnostic criteria of LQTS. The present study shows that the proposed diagnostic criteria of LQTS (6) used for clinical and research purposes among patients with unknown genotype are conservative in classifying members of the LQTS families. In clinical practice, the diagnostic criteria are always a compromise, between trying to treat those at real risk and avoiding unnecessary treatments of those without significant risk. For research purposes, various ECG and/or clinical criteria have been applied as inclusion criteria to define the presence or absence of LQTS. These criteria have typically included the duration of QTc, with the diagnostic criteria proposed by Schwartz et al. (6) receiving highest acceptance. Our data on a genetically homogenous population of LQT1 patients suggest that application of these criteria, including those of Schwartz et al. (6), to patient selection results in true positive diagnosis with a high probability of correctness; but a considerable proportion of the affected patients will be excluded. It is therefore possible that in many previous clinical studies on LQTS, based on the available diagnostic criteria, a number of affected subjects remained undiagnosed, and conclusions on clinical outcome were drawn from the most aberrant patients and their responses.

Clinical implications. Despite the improvement in diagnostic accuracy due to molecular genetics, the question of need to treat asymptomatic gene carriers remains open. It is of note that a total of 6 (20%)—two symptomatic and four asymptomatic—LQT1 patients had QT interval at or below the upper limit of normal population. Although their QT interval is still "normal," it can be speculated that the duration of repolarization in these individuals would be even shorter without the KVLQT1 gene mutation. Previously, when genetic diagnosis was not available, it was recommended that asymptomatic children with family history of LQTS and QT_c >440 ms, that is, those who were potential asymptomatic carriers of the LQTS gene, should be treated. We believe today, however, that risk assessment and decision to treat should be based on genetic analysis, if feasible, and on additional risk factors. For instance, increasing age and male gender appeared to associate with a more favorable outcome in the study of Zareba et al. (13). On the other hand, long QT interval may predict cardiac events, but its role must now be reevaluated using reference QT values for the particular population, together with other risk factors in larger genetically defined populations. Increased QT disper-

sion and relative tachycardia may represent such other risk factors predicting cardiac events. According to Zareba et al. (13), heart rate >85 beats per minute in LQTS patients older than 10 years is associated with increased risk of cardiac events, but this may not be applicable to all forms of LQTS. The clinical significance of the genetic disorder even without clinically manifest disease may become evident, for example, when a patient is exposed to QT interval prolonging drug. The knowledge of the genetic status is thus important since it enables patient counseling and avoidance of additional risk factors even when he or she is an asymptomatic LQTS carrier.

Study limitations. There were certain limitations in the present study. The study population consisted of patients with one specific mutation of the KVLQT1 gene. In spite of its critical location in the pore region of the potassium channel, other mutations of the same gene may produce quantitatively diverging alterations in repolarization phenomena. Therefore, the distribution of QT intervals or dispersion parameters of ventricular repolarization presented here cannot be generalized to all LQT1 patients without further studies.

Conclusions

Even in a genetically homogenous population, application of electrocardiographic measures using the standard 12-lead ECG only, or the clinical criteria, does not result in correct diagnosis of all cases of LQTS. In addition to causing occasional false negative diagnoses in clinical practice, we suspect that some previous investigations may have the potential bias of concentrating on the most aberrant patients only. QT duration alone appears to be a poor predictor of cardiac events even among patients possessing the same mutation. There is a need to study the interplay between genetic and environmental factors that modify the QT interval and the specific mutation types in LQTS.

References

1. Romano C, Gemme G, Pongiglione R. Aritmie cardiache rare dell'eta' pediatrica. II. Accessi sincopali per fibrillazione ventricolare parossistica. Clin Pediatr (Bologna) 1963;45:656–83.
2. Ward OC. A new familial cardiac syndrome in children. J Ir Med Assoc 1964;54:103–6.
3. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome. Prospective longitudinal study of 328 families. Circulation 1991;84:1136–44.
4. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. N Engl J Med 1992;327:846–52.
5. Saarinen K, Swan H, Kainulainen K, Toivonen L, Viitasalo M, Kontula K. Molecular genetics of the long QT syndrome: two novel mutations of the KVLQT1 gene and phenotypic expression of the mutant gene in a large kindred. Human Mutation 1998;11:158–65.
6. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome. An update. Circulation 1993;88:782–4.
7. Malfatto G, Beria G, Sala S, Bonazzi O, Schwartz PJ. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. J Am Coll Cardiol 1994;23:296–301.
8. Sagie A, Larson MG, Goldberg RJ, Bengston JR, Levy D. An improved method for adjusting the QT interval for heart rate (the Framingham Heart Study). Am J Cardiol 1992;70:797–801.
9. Puddu PE, Jouve R, Mariotti S, et al. Evaluation of 10 QT prediction formulas in 881 middle-aged men from the seven countries study: emphasis on the cubic root Fridericia's equation. J Electrocardiol 1988; 21:219–29.
10. Karjalainen J, Viitasalo M, Manttari M, Manninen V. Relation between QT intervals and heart rates from 40 to 120 beats/min in rest electrocardiograms of men and a simple method to adjust QT interval values. J Am Coll Cardiol 1994;23:1547–53.
11. Schwartz PJ. Idiopathic long QT syndrome: progress and questions. Am Heart J 1985;2:399–411.
12. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. The long QT syndrome: a prospective international study. Circulation 1985;71:17–21.
13. Zareba W, Moss AJ, le Cessie S, et al. Risk of cardiac events in family members of patients with long QT syndrome. J Am Coll Cardiol 1995;26: 1685–91.
14. Garson A, Jr., Dick MD, Fournier A, et al. The long QT syndrome in children. An international study of 287 patients. Circulation 1993;87:1866–72.
15. Statters DJ, Malik M, Ward DE, Camm AJ. QT dispersion: problems of methodology and clinical significance. J Cardiovasc Electrophysiol 1994;5: 672–85.
16. Priori SG, Napolitano C, Diehl L, Schwartz PJ. Dispersion of the QT interval. A marker of therapeutic efficacy in the idiopathic long QT syndrome. Circulation 1994;89:1681–9.
17. Wang Q, Shen J, Splawski I, et al. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. Cell 1995;80:805–11.
18. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 1995;80:795–803.
19. Schott JJ, Charpentier F, Peltier S, et al. Mapping of a gene for long QT syndrome to chromosome 4q25-27. Am J Hum Genet 1995;57:1114–22.
20. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. Nat Genet 1996;12:17–23.
21. Chambers JB, Sampson MJ, Sprigings DC, Jackson G. QT prolongation on the electrocardiogram in diabetic autonomic neuropathy. Diabet Med 1990;7:105–10.
22. Fei L, Goldman JH, Prasad K, et al. QT dispersion and RR variations on 12-lead ECGs in patients with congestive heart failure secondary to idiopathic dilated cardiomyopathy. Eur Heart J 1996;17:258–63.
23. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353–70.
24. Fridericia LS. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. Acta Med Scand 1920;53:469–86.
25. Karjalainen J, Ristola P, Reunanen A, Viitasalo M. QT interval as a cardiac risk factor in a middle-aged population. Heart 1997;77:543–8.
26. Moss AJ, Robinson J. Clinical features of the idiopathic long QT syndrome. Circulation 1992;85(Suppl 1):I140–4.
27. Day PC, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br Heart J 1990;63:342–4.
28. Linker NJ, Colonna P, Kekwick CA, Till J, Camm AJ, Ward DE. Assessment of QT dispersion in symptomatic patients with congenital long QT syndromes. Am J Cardiol 1992;69:634–8.